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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,033	07/03/2001	Mark Henry Pausch	011420102	5078

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,033	PAUSCH ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *8,10-12,14-19 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 13, 20-24, 28, 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 7/12/04, have been entered in full.

Claims 8, 10-12, 14-19, 25-27 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Claim Objections:

Claim 3 is objected to be cause it appears that the word "and" in line 2 of the claim is intended to be "in an". Appropriate correction is required.

Maintained Rejections:

Claim 29 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth previously.

In claim 29, regarding the phrase "the deletion is IC3Δ", one skilled in the art might interpret this to mean that the entire intracellular third loop has been deleted, however the specification implies, but does not state, that the term IC3Δ refers to any deletion in the third

intracellular loop and need not be interpreted as limited to the deletion of the entire loop (e.g. page 3). It is suggested to Applicant, that if it is the latter meaning that is appropriate, then the phrase "the deletion is an IC3Δ" would encompass many types of deletions in the third intracellular loop.

Applicant asserts that the discussion at page 7, would lead one to an understanding of the term. This argument has been fully considered but not deemed persuasive. The parenthetical reference of the 44 amino acid deletion referred to by applicant does not establish that the claim is limited to this particular deletion. Thus the bounds of the claim cannot be determined.

Claims 1 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996.

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the Abstract and col 3), and wherein the measuring effect of the test compound is measuring growth (see col 4).

Applicant argues that nothing at column 3 suggests introducing a mutation an intracellular domain much less for the purpose of improving the coupling of the receptor to the G-protein. This argument has been fully considered but not deemed persuasive. First, column 3 specifically teaches mutation in the intracellular domains, e.g. lines 20-25. Second, one ordinary skill in the art readily appreciates that the entire purpose of making the hybrid proteins is to

improve the functional coupling between the receptor and the G-protein because this is the very concept that allows the invention to work, i.e. to make the receptor biologically active in the yeast cell, e.g. see lines 55-67.

Claims 1-7, 20-24, 28, 29 stand rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by U.S. Patent No: 5789184, to Fowlkes, published Aug. 4, 1998, filed June 5, 1995 which claims priority to application 08041431, filed March 31, 1993, as set forth previously.

Fowlkes disclose yeast cells comprising a nucleic acid encoding a GPCR (e.g. a muscarinic receptor, that may be mutated, Col 26, L19-L25) that has been modified as a matter of routine optimization of operating parameters, i.e. such that it is improved in its functions in a cell based assay as compared to wild-type, (col 15, L29-L63), wherein the modification comprises a deletion is in one of the loops of the GPCR (col 15, L57). One of ordinary skill in the art would understand from the teachings of col 15 that the reference to "loops" at line 57 necessarily includes the third intracellular loop because it is only one of six loops. Further, the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells, see col 10, L27-44.

Applicant argues that the purpose the passages recited by the examiner do not purpose introducing mutations for the purpose of improving the coupling of the receptor to the G-protein. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art would ask what other reason would Folwkes teach conservative mutations in the receptor other than to improve the function, i.e., the coupling of the receptor to the G-protein, as this is the very essence of the assay. By referring to col 10, L27-44, the examiner is simply citing were

it is understood that the function of the receptor, and thus the modifications to it, is clearly taken to be an improvement in the agonist-induced growth of the cells.

Claim 2 stands rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996 in view of W0 92/05244, to King, published 4/2/1992, as set forth previously

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the Abstract and col 3), and wherein the measuring effect of the test compound is measuring growth arrest, a negative effect, (see col 4) or the or the induction of LacZ, a positive effect (col 3). Claim 2 however requires that the agonist increase growth. King et al. describe an identical assay where the effect of an agonist would be to either to induce LacZ or HIS3, see page 10, L14. It is old and well established that the HIS3 gene is used as an indicator gene because its induction allows yeast to grow on media lacking histidine; thus one of ordinary skill in the art would understand that King intends that the HIS3 gene would be used to produce agonist-induced growth of cells.

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to use HIS3 as a reporter gene as taught by King in the assays taught by both King and Sledziewski wherein the GPCR comprises a modification as taught by Sledziewski. The

motivation to do so is provided by King who teach that the assay can be performed with HIS3 as the reporter gene in addition to LacZ.

Applicant's arguments regarding Sledziewski have been fully addressed above. Regarding the teachings of Strader, this reference is not being relied upon in the instant rejection and the examiner's statement was merely intended to provide a road map to overcoming the rejection based on Strader. The results of Strader simply point to the great diversity and adaptability of GPCR assays.

Claim 9 stands rejected under 35 U.S.C. 103(a) as being anticipated by U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996 in view of Bonner et al., Science 237(527-537)1987 as set forth previously.

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the Abstract and col 3. Sledziewski do not specifically mention that the muscarinic acetylcholine receptor should be the rat M3 receptor. Bonner et al. (1987) describes the cloning of the rat M3 muscarinic receptor, see the Abstract and Figure 1. Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to use the rat M3 muscarinic acid receptor as taught by Bonner when practicing the

invention of Sledziewski. The motivation to do so is taught by Sledziewski teach that muscarinic acid receptor should be used in the invention, and by Bonner who provide the receptor.

Applicant's arguments regarding Sledziewski and Strader have been fully considered but not deemed persuasive for the reasons set forth above.

Claim 9 stands rejected under 35 U.S.C. 103(a) as being anticipated by U.S. Patent No: 5789184, to Fowlkes, published Aug. 4, 1998, filed June 5, 1995 which claims priority to application 08041431, filed March 31, 1993 in view of Bonner et al., Science 237(527-537)1987, as set forth previously.

Fowlkes disclose yeast cells comprising a nucleic acid encoding a GPCR (e.g. a muscarinic receptor, that may be mutated, Col 26, L19-L25) that has been modified as a matter of routine optimization of operating parameters, i.e. such that it improved in its functions in a cell based assay as compared to wild-type, (col 15, L29-L63), wherein the modification comprises a deletion is one of the loops of the GPCR (col 15, L57). One of ordinary skill in the art would understand from the teachings of col 15 that the reference to "loops" at line 57 necessarily includes the third intracellular loop because it is only one of six loops. Further, the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells, see col 10, L27-44.

Fowlkes et al. specifically teach that a GPCR from any origin can be used in the invention (e.g. col 14, line 47) and also that proteins described in Bonner et al. (1987) can be used (col 81), however, Fowlkes do not specifically mention the rat M3 muscarinic receptor.

Bonner et al. (1987) describes the cloning of the rat M3 muscarinic receptor, see the Abstract and Figure 1. Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to use the rat M3 muscarinic acid receptor as taught by Bonner when practicing the invention of Fowlkes. The motivation to do so is taught by Fowlkes who state that a protein from any origin can be used and who specifically point to the Bonner reference.

Applicant's arguments regarding Fowlkes and Strader have been fully considered but not deemed persuasive for the reasons set forth above

Claim 13 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modification that results in a 44 amino acid third intracellular loop comprising the 22 residues proximal to the 5th and the 6th transmembrane domains, does not reasonably provide enablement for other modification resulting in a 44 amino acid third intracellular loop, as set forth previously. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification indicates that deletions can be made to a variety of GPCRs wherein the remaining third intracellular loop comprises the 22 residues proximal to the 5th and the 6th transmembrane domains, resulting in a 44 amino acid third IC loop (e.g. Examples 1-4). This is a very specific teaching, yet the claims encompass any of a practically infinite number of deletions – which only need to result in a 44 amino acid third IC loop. The specification has not taught a method for the artisan to use to discover other such deletion strategies and has only offered the artisan an invitation to randomly try to find such.

The claim is, in essence, single means claim, because the claim encompasses any composition having the recited activities whereas the instant specification only discloses the single composition known to the inventor. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). The skilled artisan would not expect to readily find such other deletion mutants. As indicated above, the prior art demonstrates that many deletions diminish the efficiency G-protein activation – a property that is asserted to be necessary for the instant invention, see page 3 of the instant specification and pg 13 L10-14 of Strader (WO 96/00739) who teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G-protein.

Applicant argues that methods used to make one mutation should be sufficient to make any other. This argument has been fully considered but not deemed persuasive. The issue is not that a mutation would be difficult to make, rather the specification has failed to teach which mutations to make that will produce a protein useable in the claimed invention, i.e. one that results in improved coupling of the receptor and G-protein.

Conclusion

This application contains claims 8, 10-12, 14-19, 25-27 drawn to an invention nonelected with traverse in Applicant's response of 10/31/03. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached at (571) 272-0887.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

October 3, 2004